BREAST CANCER IN THE ELDERLY*

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BREAST CANCER in the United States is increasing. In 1990 150,000 women had breast cancer compared to 180,000 reported to have the disease in 1991.[1] There is an even steeper increase in the incidence of breast cancer in elderly women. In 1991, of the 42,000 women who died from breast cancer, more than half were older than 65.[2] In fact, the incidence of breast cancer for women over 70 is now 350 per 100,000 compared to 60 per 100,000 for women under 65.[3]

The reason for the increase in breast cancer for the elderly is not completely understood. It may be that with increased longevity in the United States, more women are exposed to factors that allow breast cancer to develop. This goes along with a theory that breast cancer is caused by events happening in the genes secondary to the external environment. The real truth about this has not yet been elucidated through research.

INCIDENCE

Although the incidence of breast cancer is higher in women older than 65, most patients seen at medical centers with breast cancer are younger. In a retrospective study from Duke University, of the 1795 patients given their primary treatment for breast cancer at the medical center over a 14-year period, 23% were older than 65 and only 6.4% were over 75.[4]

Another retrospective study of patients with operable breast cancer at Columbia Presbyterian showed that 19% were 70 years old or older.[5] Looking at these two large studies, it would be safe to say that only about 20% of patients treated for primary breast cancer at hospitals in 1992 will be older than 70 years. The actual number of elderly women with breast cancer is higher than this, since neither of these studies take into account patients with

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breast cancer who never go to a medical center. Many older patients are seen in a physician's private office and may be considered too old or ill for treatment.

Stage of Disease

Studies on breast cancer in the elderly demonstrate that most patients present to medical centers still in the early stages of their disease. In a study from the University of Nebraska, 198 patients presented with breast cancer in a 20-year period who were 80 years old or older.[6] Of these cases, 19.7% had Stage I disease and 38.9% had stage II disease; thus 58.6% had stage I or II disease. Moreover, one fifth of the patients were not staged, so that they could be in any of the four stages and perhaps even more of these patients would have been stage I or II had these patients been staged. Patients with positive lymph nodes were equally divided between having 1 to 3 positive lymph nodes and 4 or more positive lymph nodes. This again reflects the trend toward earlier stages at diagnosis.

In the study previously cited from Columbia Presbyterian, even more elderly patients were stage I or stage II at presentation, with 76% in these early stages. The National Cancer Institute Division of Cancer Prevention and Control reviewed data on 125,000 women diagnosed with breast cancer from 1973 to 1984.[7] This study showed that in women 75 to 84, 51.4% had localized breast cancer (Stage I) and 35.1% had regional disease (Stage II), which means that approximately 86% were in stages I and II. For patients more than 85 years old this decreased slightly, 79.9% having localized or regional disease. Another study from the Massachusetts General Hospital of 80-year-old and older women presenting with breast cancer during one decade had 29% in stage I and 42% in stage II, or 71% in the loco-regional stages.[8] Most studies seem to agree that elderly women with breast cancer most commonly present in either a stage I or II level.

Estrogen Receptors

Estrogen receptor analysis has not been reported in many studies done on breast cancer in the elderly. The large study from Columbia tested 369 patients for estrogen receptors (ER), with 291 or 81% ER positive (ER level of greater than 10 fmol/mg). It is known that 60% of breast cancers in postmenopausal women will be ER positive, while only 30% of premenopausal women will have ER positive breast cancer.

One theory to explain this increase in ER positive tumors among older women is that tumors developing late in a woman's life are not exposed to

the stimulation of circulating estrogen present in premenopausal women. Thus, these tumors are less likely to be hormone resistant.[9]

All evidence points to a higher rate of ER positive tumors (70%–80%) among the elderly and to tumors that are more hormone sensitive.

Surgical Treatment

Surgical treatment for breast cancer in any age group has changed over the last 15 years. Certainly in the 1960s, prior to the National Surgical Adjuvant Breast Project Study, most patients received a radical mastectomy for stage I or II breast cancer, based on Halsted's work early in the 20th century. After this large trial of radical mastectomy versus total mastectomy demonstrated no difference in survival, most surgeons dropped the concept of radical mastectomy and began doing modified radical mastectomies, saving the pectoralis major muscle.[10]

The same study group again led a revolution in breast cancer surgery by comparing lumpectomy to mastectomy. That study, now mature over eight years, shows no difference in outcome between lumpectomy plus radiation versus mastectomy.[11] Because of these trends in research, breast conserving procedures are more frequently performed and the idea that the breast must be removed for a better chance at cure is no longer true.

However, all of these studies were done in women younger than 70, and most were done in women younger than 65. What is true for the women in that age category may not hold true for older women. In fact, many studies in the elderly show that women are treated most often with mastectomies. In the study from Columbia Presbyterian, 355 of 479 patients (74%) had modified radical mastectomies and 12 more had total mastectomies. In a study from British Columbia, 76 out of 150 patients had mastectomies[12] and in the Nebraska study 148, almost three quarters of the patients had mastectomies.

A Massachusetts General Hospital study reviewed the records of 150 women who were 80 years old or older admitted with the diagnosis of breast cancer. Nineteen of the 150 had radical mastectomy (this study reviewed charts from 1970–1980 which may explain why so many had radical mastectomies), 41 had modified radical mastectomy, 22 had simple mastectomy, and 16 patients had lumpectomy. The reasons for the lumpectomy in these 16 patients were multifactorial. Seven had a lesser procedure because of poor medical health, and four more refused radiation therapy or hormones after the lumpectomy. Thus, only five of the 16 patients had lumpectomy and radiation therapy as an elective alternative to mastectomy. Yet the study

implies that the survival was worse in the lumpectomy patients, without taking into account differences in general health among these patients.

In the Columbia study, although most women had mastectomies, 108 patients did have lumpectomies and the results showed no difference in survival depending on surgical treatment.

Three English studies compared surgery alone to Tamoxifen alone. One was done at St. George's Hospital in London.[13] In 1982 they randomized all patients over 70 years old who had a resectable breast cancer to have surgery, either a wide local excision or total mastectomy, versus treatment with Tamoxifen only at 20 mg/day for 2 years. One hundred sixteen patients were entered into this study. The mean age was 75.4. Results show no difference in survival or local recurrence between the two groups in three years. Both groups were eligible for crossover treatment if they failed the first treatment. Thus, patients with surgery who had local recurrences would receive Tamoxifen, and those on Tamoxifen who progressed or relapsed would have surgery. This study brought into question the necessity of extensive surgery for this patient population.

Another study from Scotland treated 113 women age 70 years old or older with Tamoxifen alone as primary treatment. They were followed for five years.[14] Thirty-eight women had complete tumor response to Tamoxifen, 17 had a partial response, and there was no change in 34 women. Only 24 had progressive disease. When patients had progressive disease or relapse they were treated with surgery. The five-year survival rate was 49.4% for all patients, but was much higher for those showing an initial complete response. The conclusion was that Tamoxifen was a good alternative therapy to surgery for operable breast cancer.

Another study from Edinburgh treated 100 elderly patients with localized breast cancer with Tamoxifen alone. Median follow-up was 59 months. Sixty-eight of the 100 patients responded, 10 had progressive disease, and 22 had stable disease. Survival was better than that of an unmatched historical control group treated by mastectomy.[15]

These studies all underscore the controversy about surgical treatment in the elderly by questioning the necessity of a mastectomy.

Hormonal Therapy

Tamoxifen is a widely used hormone which has come into practice in the United States in the last 15 years. As in previous randomized studies, most studies of Tamoxifen have been in younger women, but a few have studied Tamoxifen in elderly age groups.

The largest study in the United States was done by the Eastern Cooperative Oncology Group known as ECOG.[16] This involved 170 patients: all had mastectomies and all were lymph node positive and estrogen receptor positive (if receptors status had been done). They were randomized between Tamoxifen alone or placebo alone. The mean age of patients in this study was 71 and only 25% were older than 75. More than half of the patients had three or fewer involved nodes, and 85% were known to be estrogen-receptor positive. Disease-free survival at four years was 76% for those on Tamoxifen versus 53% for the placebo group ($p = 0.0004$). Overall survival did not differ between the groups at four years. Thus, a blinded placebo study showed a Tamoxifen benefit for disease-free survival in patients older than 65 with positive lymph nodes.

The International Breast Study Group, formerly known as the Ludwig Group, in Europe conducted a study from 1978 to 1981 that included 349 patients all older than 65.[17] All had positive lymph nodes and all had a mastectomy prior to randomization. Patients were randomized to receive either Prednisone and Tamoxifen for one year following surgery or to be observed after surgery. The median age of patients in this study was 70, and most women had only one to three positive lymph nodes. Only 35% had known positive ER receptor status. This study was striking in that disease-free survival and the incidence of contralateral breast cancer were significantly better in the treatment group. Here again, a large randomized study of a relatively older age group showed a benefit for adjuvant Tamoxifen.

These two large prospective studies were both carried out in node-positive women. Most other studies were retrospective analyses of elderly women with breast cancer. In the Columbia study, a retrospective analysis, most women did not get Tamoxifen. Of the patients who were ER positive with negative lymph nodes, only four patients died of breast cancer. It is interesting that of the 106 patients who died in the Columbia study, only 50 died of breast cancer and 56 died of causes other than breast cancer, and that of 102 recurrences 63 were cancers in the contralateral breast.

Both this Columbia study and the ECOG study demonstrate that one factor in breast cancer among the elderly is a high incidence of recurrence in the contralateral breast.

A recently published *Lancet* meta-analysis of all of the randomized studies done in women with breast cancer, involving more than 75,000 women, entered into studies worldwide.[18,19] The meta-analysis showed a marked benefit from Tamoxifen in women older than 70 regardless of estrogen status,

and showed a decreased incidence of contralateral breast cancers in those women getting Tamoxifen.

With the high ER positivity rate and the high incidence of contralateral breast cancer among elderly patients, Tamoxifen would seem to be the ideal drug for this group.

DISCUSSION

Breast cancer among the elderly is increasing in incidence. More than 20% of patients who present for care with breast cancer are older than 70, and currently more than 50% of patients who die of breast cancer are older than 65. Most elderly patients with breast cancer have only stage I or II disease at presentation. Most patients will be ER positive. Lymph node positivity and ER status remain the most important prognostic indicators whatever the age of the patients.

Although mastectomy is the common surgical treatment at this time, it is not clear that it is necessary in the older age groups. Many studies have shown that less radical surgery plus Tamoxifen may be equivalent to usual surgical treatment, although most studies have not been in a randomized prospective fashion.

Almost all studies of Tamoxifen for elderly patients have shown a benefit for Tamoxifen, but no randomized studies have reviewed Tamoxifen for elderly patients with breast cancer but with negative lymph nodes.

It remains a future task to do appropriate and accurate studies of breast cancer in the elderly to learn which groups should get Tamoxifen and which groups should have less surgery than mastectomy. However, with the publication of the meta-analysis,[18,19] it seems that Tamoxifen should be given to all women with breast cancer over the age of 65 as at least one part of their treatment. It would be appropriate at this time, with the increasing incidence of breast cancer among the elderly, for the cooperative cancer study groups to pay more attention to breast cancer in the elderly and to design studies to answer the particular questions that have to be asked for this patient population.

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